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Use of Statin Therapy in Children and Adolescents Diagnosed with Familial Hypercholesterolemia to Prevent Premature Cardiovascular Disease

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Abstract

Familial hypercholesterolemia (FH) is a common genetic disorder that is associated with premature cardiovascular disease (CVD). CVD is the leading cause of death and morbidity in the United States, and although it generally becomes clinically evident in adults, the development of atherosclerosis has its origins in childhood. Unfortunately, the majority of children and adolescents with FH go undiagnosed and untreated as signs and symptoms of CVD only develop after decades of hypercholesterolemia. This review of literature will discuss the importance of early diagnosis and treatment of FH, and how statin therapy needs to be initiated in early childhood before significant atherosclerosis develops.

The significance of this problem and basis of the literature review is demonstrated by an outpatient clinical case involving a 24-year old male requesting to have his cholesterol levels checked after his father passed away suddenly from a heart attack at age 46. This case is a great example of how many young patients can go undiagnosed and untreated with FH because they are asymptomatic. This case led to the systematic search to determine that statin therapy should be initiated in childhood in individuals with a diagnosis of FH.

This literature review will describe a model of care for FH focusing on the use of statin therapy in children and adolescents. With the availability of effective statin therapy, practitioners are in a place where they can improve the outcomes of this disorder by detecting and managing hypercholesterolemia in childhood, thereby preventing premature cardiovascular disease.

Keywords: children, adolescent, familial hypercholesterolemia, genetic, statin, therapy

Significance of Initiating Statin Therapy in Children and Adolescents

Familial hypercholesterolemia (FH) is a common genetic disorder with a prevalence of 1:500 in the general population (Justo, 2012). It is a disorder of low-density lipoprotein cholesterol (LDL-C) metabolism, which is coupled with the onset of vascular changes associated with cardiovascular disease (CVD) in childhood (Wiegman et al., 2015). Practitioners must be vigilant when taking a patient's family history with regard to early CVD. Thus, when patients with early CVD are assessed and treated, all family members, including children under 10 years of age, must be investigated. Because the atherosclerotic disease process associated with FH begins in childhood, practitioners should strongly consider pharmacological treatment with statin therapy in this population. Therefore, once affected children are identified, a plan of care including lifestyle changes and statin therapy should be initiated.

Currently, there is broad consensus that statin therapy is the treatment of choice in children diagnosed with FH, and it should be commenced by 10 years of age. Statin therapy may also be indicated in children with FH aged 8 or 9 years with a family history of premature CVD, additional CVD risk factors and LDL-C persistently greater than 190 mg/dL after six months of non-pharmacological treatment such as diet and lifestyle changes (Braamskamp, Wiegman, & Wijburg, 2012). According to Justo 2012, the initial therapeutic goal with statin therapy is to lower serum LDL-C levels to values less than 130 mg/dL.

Statins are the preferred agent for treating FH in childhood as they are safe and effective in all age groups. They act by inhibiting cholesterol synthesis, which in turn generates an increase in the number of LDL receptors and results in increased clearance of LDL-C from the circulation (Hardcastle et al., 2015). Several randomized controlled trials have shown clinically

significant reduction in both total and LDL-C in children treated with statin therapy (Justo, 2012). According to Justo (2012), a 2010 Cochrane review estimated the difference in LDL-C reduction was -26.5% in children treated with statin therapy.

To demonstrate, the case scenario presented in the following section signifies the importance of diagnosis and treatment of FH in early childhood and adolescence. The case scenario involves a 24-year old male presenting to the clinic requesting to have his cholesterol levels checked due to a family history of premature cardiovascular disease. His father had recently passed away from a heart attack while shoveling snow at the age of 46. In addition, the patient's family history included a brother with known high cholesterol. The patient was asymptomatic, but in addition to his family history of premature CVD, he had other risk factors for heart disease such as an elevated BMI, heavy alcohol use, diet high in cholesterol and insufficient aerobic exercise. His fasting lipid panel verified the diagnosis of FH and he was started on high-intensity statin therapy with the goal of preventing an early adverse cardiovascular event. The case is discussed in detail in the following section.

Case Report

For the purpose of anonymity, the patient in this case report will be called Brad. Brad is a 24-year old male who presents to the clinic requesting to have his cholesterol levels checked due to a family history of high cholesterol and premature CVD. His mother encouraged him to get his cholesterol levels checked after the recent passing of his father. Brad's father recently passed away at the age of 46 from a heart attack while shoveling snow. In addition, his brother has hyperlipidemia and is on cholesterol-lowering therapy. His mother has no known

medical problems and Brad is otherwise feeling healthy. The entire history was obtained from the patient during the visit.

History

Brad has a history of allergic rhinitis for which he uses Zyrtec as needed. He has no other known medical history and does not take any prescription medications. His past surgical history includes a tonsillectomy with adenoidectomy at age four. He is currently employed as an emergency medical technician (EMT) and works 12-hour shifts with the ambulance crew. Due to the nature of his shift work, Brad admits to eating an unhealthy diet consisting of fast food about four to five times per week. He lifts weights an average of four to five days per week but does not take part in any high-intensity cardio exercise. He denies any smoking history or use of smokeless tobacco, but he does admit to drinking alcohol socially one to two weekends per month in which he consumes five to six drinks. In addition, he reports drinking two beers each evening at home.

Review of Systems

During the exam, a complete review of systems was completed. Brad reports some "bumps" on his left elbow and left knee that are not bothersome. The remaining systems were reviewed with no indication of any abnormalities. Brad denies any symptoms of fatigue, chest pain, shortness of breath, dizziness, palpitations or visual disturbances. He is not having any gastrointestinal or genitourinary complaints. He denies any depression, weight loss or anxiety.

Physical Exam and Diagnostic Studies

A focused physical exam was completed with the following findings. Vital signs revealed a blood pressure of 110/54 mmHg, pulse 62 beats per minute, temperature 32.1 degrees Celsius, weight of 200 pounds, and height of 6 foot 1 inch. The vital signs were normal with the exception of his BMI which is elevated 26.4. According to the National Heart, Lung, and Blood Institute 2016, he is overweight. The physical examination findings were unremarkable. Heart sounds were S1, S2 with regular rate and rhythm. Lung sounds were clear throughout lung fields. Pulses were 2+ in all four extremities. Carotid pulses were 2+ bilaterally without bruits. The skin on his left elbow and left knee appears normal in color, texture and appearance.

Due to the patient's family history and CVD risk factors, the diagnostic studies done included lab testing consisting of a fasting lipid panel and a comprehensive metabolic panel (CMP). The CMP revealed a normal blood glucose level of 86 mg/dL ruling out Diabetes Mellitus, and normal liver enzymes indicating healthy liver function. If statin therapy is anticipated, it is necessary to have normal liver function prior to starting the medication. Furthermore, the liver enzymes were relevant due to the patient's report of above moderate alcohol use. All other values within the CMP were within normal limits. On the contrary, the fasting lipid panel revealed a total cholesterol level of 310 mg/dL, triglycerides 140 mg/dL, HDL 60 mg/dL and LDL 209 mg/dL, indicative of hypercholesterolemia.

Management of Care

Due to Brad's family history of hyperlipidemia and premature CVD-related death, and his own elevated total cholesterol level with a LDL cholesterol greater than 190 mg/dL, he was diagnosed with familial hypercholesterolemia. Although Brad did not have clinical evidence of

atherosclerotic cardiovascular disease, his risk factors, family history and LDL level made it appropriate to treat him with high intensity statin therapy. Under those circumstances, he was placed on Atorvastatin 40mg by mouth daily. He was educated on the side effects of the medication, including commonly occurring myalgia's.

Unfortunately, Brad is at high risk for cardiovascular disease based on his LDL-cholesterol alone. Therefore, in addition to the high intensity statin therapy, he was educated on non-pharmacological treatment such as diet and lifestyle changes. He was educated on weight loss and dietary reduction in total and saturated fat. He was also encouraged to increase his intake of dietary fiber, complex carbohydrates and unsaturated fats. Lastly, he was encouraged to engage in aerobic exercise with a goal to reach his target heart rate of 100-170 beats per minute, and maintain that heart rate for 30 minutes five days per week.

He will follow up in three months as per current guidelines to repeat a fasting lipid panel and recheck his liver function tests after the initiation of statin therapy. If indicated, his Atorvastatin may be increased to 80mg by mouth daily. His skin complaints can be reassessed at his follow up visit if they are still an issue. Brad verbalized understanding of the management plan and will schedule a three-month follow up visit. He is encouraged to call or come back to the clinic in the meantime with any questions or concerns.

Brad's case study demonstrates the opportunity for early diagnosis and treatment of asymptomatic patients with FH, which is essential in preventing premature adverse cardiovascular outcomes. For this reason, healthcare providers need to be vigilant when assessing patient's CVD risk factors and family history. Routine wellness visits warrant an opportunity to screen, diagnose, educate and prevent unwanted complications. If Brad had not

presented to the clinic requesting screening, he may have ended up with premature adverse cardiovascular outcomes such as stroke, myocardial infarction, peripheral vascular disease and much more. Thus, it is the responsibility of the healthcare provider to screen every patient, including children and adolescents, for early CVD risk factors with each visit to ensure statin therapy is initiated at an optimal time if indicated.

Search Strategies

In order to find evidence to support the use of statin therapy in children and adolescents with FH, an online search was conducted using the University of North Dakota Harley French Library website. Two different search engines were utilized to conduct the research, PubMed and CINAHL.

The first search engine utilized was CINAHL, which stands for the Cumulative Index to Nursing and Allied Health Literature. CINAHL headings were used to concentrate the search. The first headings searched were "familial hypercholesterolemia" AND "statin therapy" and "children". This search yielded nine articles. Following this, the English language limit was added, still yielding nine articles. Titles were scanned for relevance and six articles were reviewed in detail. Five were found to be relevant to the search topic.

Next, another search using "familial hyperlipidemia" AND "treatment" AND "children" yielded 17 articles. Results were further limited to English language and year which resulted in nine articles. Eight of the articles were thoroughly reviewed and five were found relevant to the clinical question. Lastly, a review of reference sections of each relevant article yielded one additional article relevant to the search topic.

Literature Review

FH is the most common and serious disorder of lipid metabolism that leads to premature coronary heart disease (Martin, Coakley, Forbes, Sullivan & Watts, 2013). Worldwide, one baby is born with FH every minute (Wiegman et al., 2015). Children with FH have markedly elevated plasma levels of LDL cholesterol from the time of birth, which in turn strongly predisposes them to progressive atherosclerosis throughout childhood, and premature CVD in adulthood.

The prevalence of FH is approximately 1 in 500, but the majority of children and adolescents with FH are undiagnosed as signs and symptoms only develop after decades of hypercholesterolemia (Braamskamp et al., 2012). FH left untreated results in fatal coronary heart disease in 50% of males and 20% of females by 60 years of age (Martin et al., 2013). According to Martin et al., 2013, statins reduce LDL-C levels by up to 50%, and are appropriate to use in boys after 10 years of age and in girls after menarche. Therefore, if FH is diagnosed and treated early in childhood, these individuals can have a normal life expectancy.

FH is diagnosed based on certain criteria including an elevated LDL-C level plus a family history of premature CVD, and/or a genetic diagnosis of FH from DNA testing (Wiegman et al., 2015). Unfortunately, FH continues to be underdiagnosed and undertreated nationwide as screening and treatment are not consistently implemented. According to Hardcastle et al. (2015), evidence has proven that exposure to moderate hypercholesterolemia increases the long-term risk of having an adverse cardiovascular outcome. And, given the lifelong benefit of low LDL-C levels, there is a vital need to identify and treat children with FH at an early age to maximize the therapeutic benefit of statin therapy. Not to mention, statins are safe and effective in lowering LDL-C in children, restoring endothelial function, and regressing the thickening of the vessel walls at a young age (Wiegman et al., 2015).

Unfortunately, in patients with FH and increased LDL-C levels, a diet alone is generally insufficient (Kools, Kennedy & Engler, 2008). Therefore, if cholesterol levels are not significantly reduced after six months of lifestyle modification, pharmacological therapy should be considered. The National Heart, Lung and Blood Institute (NHLBI 2016), recommends that statin therapy should be an adjunct to diet to lower LDL-C levels in adolescent boys and postmenarchal girls ages 10-18 with an LDL-C greater than 190 mg/dL, or LDL-C greater than 160 mg/dL with family history of premature CVD and two or more risk factors for CVD. Risk factors for CVD include, but are not limited to: hypertension, cigarette smoking, body mass index (BMI) greater than the 97th percentile, diabetes and kidney disease (Muir, George, & Whitehead, 2012). For children aged 8 or 9 years with LDL-C greater than 190 mg/dL after six months of diet, together with a positive family history or additional risk factors, statin therapy may also be initiated (NHLBI, 2016). The NHLBI (2016), recommends the initial therapeutic goal for children placed on statin therapy, is to lower serum LDL-C levels to values less than 130 mg/dL. Whereas, according to Martin et al., (2013), an ideal LDL-C level is less than 110 mg/dL.

Indeed, statin therapy is the foundation of FH management. According to Wiegman (2014), Simvastatin, Lovastatin, Atorvastatin, Pravastatin, Fluvastatin and Rosuvastatin are approved in the United States (US) for use in children with FH. In fact, in the US these medications are approved from age 10 years. For children aged 8-10 years, Pravastatin 20 mg is the only drug approved by the US Food and Drug Administration (FDA). It is important to realize that the short-term efficacy and safety of these statins, including during puberty, has been confirmed. Braamskamp et al. (2012), found that several clinical trials have proven that no

significant differences regarding adverse events were reported between statin-treated and placebo-treated children. Moreover, there were no differences reported in growth or sexual development or in laboratory results such as liver enzymes or creatinine kinase (CK) levels.

Upon beginning therapy, the choice of a particular statin is a matter of preference. Martin et al. (2013) mentions that Pravastatin, Fluvastatin and Simvastatin are all short acting and are best taken at bedtime, as most endogenous cholesterol is produced overnight. Whereas, Atorvastatin and Rosuvastatin are more potent statins with a longer duration of action so they can be taken at any time of day, but their use should be reserved for more severe forms of FH (Martin et al., 2013). Treatment should be initiated at the lowest recommended dose given once daily, and titrated up according to the LDL-C lowering response and tolerability. Most of the reduction in LDL-C occurs at lower doses, with increased doses yielding small reductions in LDL-C and increasing the risk of long-term side effects due to greater medication exposure (Vuorio, 2014). Although there is no evidence supporting an absolute target LDL-C in children with FH, many guidelines recommend a target LDL-C level of less than 130 mg/dL from age 10 years, or a 50% reduction in pre-treatment LDL-C levels for children 8-10 years of age (Wiegman, 2015).

It is important to note that adverse effects can occur with statin use. Therefore, it is critical to inform patients of potential adverse reactions and monitor them closley. McCrindle et al. (2007) suggests that prior to initiating statin therapy, healthcare providers should measure a baseline CK level and liver enzymes, including an aspartate transaminase (AST) and alanine transaminase (ALT) level. And, inform patients of adverse reactions that include elevated liver enzymes, CK levels and myopathy (muscle cramps and/or weakness). On rare occasion,

myopathy can progress to rhabdomyolysis. For this reason, instruct patients to report all adverse effects, including myopathy immediately. If myopathy is present, the statin should be stopped and the CK level assessed. According to McCrindle et al. (2007), if the CK level is 10 times above the upper limit of normal, consider it worrisome. However, CK levels can be increased in children who are actively participating in contact sports, so elevated CK levels shouldn't automatically be attributed to statin use. Then, repeat the CK approximately two weeks after stopping therapy, if it has returned to normal, the same statin may be restarted at a lower dose or a new statin can be trialed (McCrindle et al., 2007). Likewise, the worrisome threshold for ALT and AST is three times above the upper limit of normal (McCrindle et al., 2007). If abnormalities in the liver enzymes arise, stop the medication, recheck the levels in two weeks, and restart the same statin at a lower dose or a new statin if the levels have returned to normal.

As a matter of fact, recommendations for monitoring the safety and tolerability of statin therapy in pediatric patients with FH are similar to those in adults. After one month of statin therapy with no adverse drug reactions, measure a fasting lipid profile, CK, ALT and AST and compare results to baseline values (McCrindle et al., 2007). If target LDL levels are achieved and there are no laboratory abnormalities, continue statin therapy and recheck in eight weeks and then every three to six months (McCrindle et al., 2007). If target LDL levels are not achieved with the starting dose, double the dose and repeat the blood work in four weeks. Continue to titrate up to the maximum recommended dose until target LDL levels are achieved. In addition to laboratory values, monitor growth, sexual maturation and Tanner staging.

Moreover, adolescent females must be warned about the contraindication of statins in pregnancy and should consequently be counselled to suspend therapy when contemplating

pregnancy. According to Wiegman et al. (2015), statins should be discontinued three months before planned conception and during pregnancy and lactation. However, women who become pregnant accidentally while taking a statin should be reassured that the likelihood of fetal complications is small (Wiegman et al., 2015). Referral to an adolescent medicine or gynecologic specialist is more than appropriate.

All things considered, statin treatment is an efficient lipid-lowering therapy in children and adolescents with FH. Vuorio et al. (2104) found that several meta-analyses and a Cochrane systematic review have confirmed that statins are both effective and safe in the short to medium term in children and adolescents, but the longer term safety of these medications in this age group remains to be established. The average follow-up time in clinical trials was only six months, and the longest follow up was for two years (Vuorio et al., 2014). For that reason, large long-term randomized controlled trials are needed to establish the long-term safety issues of statins.

The most common adverse effects that have been reported in children on statin therapy are: gastrointestinal symptoms including abdominal pain, constipation and diarrhea, skin rashes, sleep disturbance and headaches (Martin et al., 2013). In most cases, Martin et al. (2013) reports that side effects occur in the early phases of treatment and resolve spontaneously without needing to change the medication. Furthermore, it is unusual to develop side effects to statin therapy if it has been tolerated for months or years. As a matter of fact, there is no evidence to support the development of tolerance, dependence or toxicity after prolonged use.

To emphasize, Vuorio (2014) found that several meta-analyses and a Cochrane systematic review have reported on statin therapy in children with FH. And, in terms of lipid

lowering, these drugs are as effective in children as in adults, with mean LDL-C reductions of 23% to 40% on average depending on the dose and type of statin prescribed. Not to mention, adverse effects do not appear to be increased in children over those noted in clinical studies in adults (Vuorio, 2014). Nonetheless, an issue of particular concern is whether statin treatment has any potential impact on development. Kusters et al. (2014) found clinical trials that have spanned the age range of pubertal development with no impact on sexual or physical maturation. In addition, only rarely was there the risk of a high increase in liver and muscle enzymes and this risk was similar in both the statin and the control groups. There were no clinically important differences in the risk of myopathy or clinical adverse events between the groups (Kusters et al., 2014). Another key point is that families reported no problems with quality of life or anxiety due to drug therapy. In fact, children reported that taking medication made them feel safer (Vuorio, 2014).

Overall, several clinical studies have indicated the beneficial effect of statins on LDL-C levels and markers of premature atherosclerosis in children with FH, as well as their safety. Future clinical studies should address the long-term safety and tolerability of statins as well as the reduction in adverse cardiovascular outcomes in adulthood in patients with FH. Until then, the benefits and risks of early initiated drug treatment should be carefully considered for each individual.

Learning Points

- Familial hypercholesterolemia (FH) is the most common and serious disorder of lipid metabolism that leads to premature coronary heart disease. The prevalence is 1:500 with one baby being born with FH every minute worldwide. Untreated, FH results in fatal

coronary heart disease in 50% of males and 20% of females by 60 years of age (Martin et al., 2013).

- Statin therapy is the foundation of FH management. They have proven to reduce low-density lipoprotein cholesterol levels by up to 50% and are appropriate to use in boys after 10 years of age and in girls after menarche (Martin et al., 2013). And, if FH is diagnosed and treated early in childhood, these individuals can have a normal life expectancy.
- Treatment with statins should be initiated at the lowest recommended dose given once daily, and titrated up according to the LDL-C lowering response and tolerability. Routine monitoring of laboratory values, growth, sexual maturation and side effects is crucial.
- Clinical trials have proven that statin treatment has no impact on sexual or physical maturation. And, there have been no clinically significant differences in the risk of myopathy or adverse events between the statin and control groups.
- Statins are both effective and safe in the short to medium term in children and adolescents, however, large long-term randomized controlled trials are needed to establish the long-term safety issues of statins. Likewise, further studies are needed to determine the optimal age of initiation of statin treatment in children.

Practice Recommendations

Practitioners must be vigilant when taking a family history with regard to early CVD. Because the atherosclerotic disease process associated with FH begins in childhood, practitioners should strongly consider pharmacological treatment with statin therapy in this population. So,

once affected children are identified, a plan of care including lifestyle changes and statin therapy should be initiated.

The NHLBI (2016) has recently published guidelines on the approach to CVD in childhood. According to NHLBI (2016), the initial step in treatment of FH is lifestyle modification, including dietary changes with limited saturated fat cholesterol intake. If lifestyle adjustment alone fails to sufficiently lower serum LDL-C levels, which is very likely in children with FH, statin therapy can be initiated in children as young as age 8 years or older. Once treatment is started, it should be continued for life; however, long-term follow-up studies on safety are lacking.

It is important to realize that optimal health care management for children with FH needs to be provided through a multidisciplinary approach, including primary care and specialty pediatric care providers. The decision regarding when to initiate drug therapy to reduce LDL cholesterol levels in children and adolescents is a balance between the benefits of starting treatment before the onset of significant disease versus the risks of therapy.

The age of the child, the family history of CVD, the level of LDL cholesterol and the views of the family are all critical to the decision-making process. Children and adolescents being treated with statins should be carefully monitored and followed up by their healthcare providers into adulthood.

Conclusion

In conclusion, there is strong evidence that the process of atherosclerosis originates in childhood and that risk factors such as hypercholesterolemia are related to subsequent CVD. In

order to prevent CVD later in life, identification of children with FH should start at an early age. Encouraging results have been obtained from clinical trials of statins in children and adolescents with familial hypercholesterolemia; however, long-term safety issues remain of concern, as does impact on clinical disease into adulthood. Further studies are needed to determine the optimal age of initiation of statin treatment in children with FH, as well as address the long-term safety and tolerability of statins and reduction of CVD in adulthood. Until then, the benefits and risks of early initiated drug treatment should be carefully considered for each individual.

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